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Editorial

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High Anti-Tumour Necrosis Factor Trough Concentrations – Only a Cost Issue or Also Hidden Dangers Ahead?

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The most common paradoxical manifestations related to tumour necrosis factor (TNF) antagonists include psoriasiform skin lesions and the occurrence of arthralgia, which have been observed in patients with Crohn's disease and ulcerative colitis treated with anti-TNFs.[1] Nevertheless, these drugs are successfully used to treat patients with psoriasis and rheumatoid arthritis. Given that these symptoms can also occur as extra-intestinal manifestations of inflammatory bowel disease (IBD), their management is challenging.

Drug exposure has been brought forward as a contributing factor but has never been studied in detail. In this issue of JCC, two studies from the Netherlands[2] and France[3] have sought to prospectively evaluate the association between TNF antagonist trough concentrations (i.e. the serum drug concentration just before the next administration of drug) and the occurrence of drug-induced paradoxical manifestations. Outcome measures included health- and disease-related quality of life questionnaires completed by the patient for the study by Brandse et al.[2] and a physician's assessment and confirmation by a specialist (dermatologist or rheumatologist) for the study by Coutzac et al.[3]

Both studies enrolled patients with IBD on anti-TNF maintenance therapy (infliximab or adalimumab for the Dutch study and infliximab for the French study). The study by Brandse et al. ruled out active disease by measuring faecal calprotectin and C-reactive protein (CRP) at baseline, whereas in the study by Coutzac et al. patients with various disease states were included. Interestingly, in the French study a trend towards lower trough concentrations was observed for patients with arthralgia compared with controls, possibly related to uncontrolled inflammation and extra-intestinal symptoms, rather than drug-induced paradoxical manifestations. Indeed, higher CRP concentrations were observed in cases than in controls. As also mentioned in the study by Brandse et al., among those patients who reported adverse symptoms there were two types: patients who experienced symptoms in the first days after anti-TNF administration (possibly related to immunological response mechanisms) and those who developed symptoms in the days before the next administration (possibly due to subclinical relapsing disease activity).

Despite these differences in patient populations, both studies concluded that psoriasiform skin manifestations and arthralgia were not associated with higher drug trough concentrations. Unfortunately, the relatively small sample size in both studies precluded meaningful subgroup analyses. Nevertheless, the current studies confirm results from a previous large retrospective cohort study of 604 IBD patients treated with anti-TNF, in which, in addition to trough concentrations, no difference was observed in the cumulative dose of infliximab between patients developing psoriasiform skin lesions and those who did not.[4]

Although the results were straightforward, one can argue whether in this case trough concentrations are the most appropriate measures to evaluate overall drug exposure, as peak concentrations or area under the curve could have been better pharmacokinetic parameters to investigate. Trough concentrations have been shown to be valuable in guiding individualized dosing in IBD patients responding to maintenance infliximab therapy. Especially in the setting of supra-optimal drug concentrations, therapeutic drug monitoring can guide dose reduction to achieve an optimal exposure level and reduce drug costs.[5] Besides cost savings, this might also have a beneficial influence on the patient's quality of life as an association between supra-optimal drug concentrations and impaired quality of life was observed in the study of Brandse et al.[2] Although statistically significant, the question remains whether the difference in IBD questionnaire score between patients with high versus low drug exposure (176 and 187 respectively) is clinically meaningful.

In conclusion, when defining drug-induced arthralgia, underlying intestinal inflammation should be ruled out by an objective marker such as CRP or faecal calprotectin as patients with symptoms due to active disease, paradoxically, might benefit from a dose increase. It is clear that, for now at least, the true value of

therapeutic drug monitoring lies in maximizing the cost-benefit of anti-TNF therapy, rather than in preventing and treating safety-related manifestations.

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Author Contributions

Both authors drafted and critically revised the manuscript and approved the final version.

Conflict of Interest

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